Int J Clin Exp Med 2015;8(2):2471-2475
www.ijcem.com /ISSN:1940-5901/IJCEM0004721

Original Article

STAT4 rs7574865 polymorphism contributes to the risk of type 1 diabetes: a meta analysis

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Received December 11, 2014; Accepted February 6, 2015; Epub February 15, 2015; Published February 28, 2015

Abstract: The signal transducer and activator of transcription 4 (STAT4) rs7574865 polymorphism has been indicated to be correlated with type 1 diabetes (T1D) susceptibility, but study results are still debatable. Thus, a meta-analysis was conducted. The electronic databases PubMed, Embase, CNKI, and Web of Science (ISI) were searched to find eligible studies. Data were extracted and pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated. A significant association was found between STAT4 rs7574865 polymorphism and T1D risk (OR=1.30; 95% CI, 1.13-1.48; P<0.01; I^2=73%). Significant associations were also found in Asians (OR=1.33; 95% CI, 1.04-1.71; P=0.02; I^2=60%) and Caucasians (OR=1.26; 95% CI, 1.08-1.47; P<0.01; I^2=74%), respectively. This association was also positive in the pediatric patients (OR=1.41; 95% CI, 1.19-1.68; P<0.01; I^2=46%). Moreover, we found that STAT4 rs7574865 polymorphism was associated with early-onset T1D risk (OR=1.43; 95% CI, 1.16-1.77; P<0.01; I^2=0%). This meta-analysis suggested that the STAT4 rs7574865 polymorphism may be associated with T1D development.

Keywords: Type 1 diabetes, signal transducer and activator of transcription 4, genetics

Introduction

Type 1 diabetes (T1D) is an organ-specific autoimmune disease characterized by the selective destruction of pancreatic β-cells. It varies from 57.4 cases/100000 per year in Finland to 0.6 cases/100000 per year in India [1]. The incidence of T1D varies among different countries, which reflects the roles played by genetic and environmental factors in the ultimate expression of the disease [2].

Members of the signal transducer and activator of the transcription (STAT) family are transcription factors that mediate the signaling events of many cytokines in immune and nonimmune cells [3, 4]. The STAT protein family member activated by interleukin-12 via its receptor that has an essential downstream role in Th1 cell differentiation and proliferation. STAT4 is also involved in the development of a newly discovered subset of Th17 cells, which display a dominant role in autoimmunity-associated inflammation, including T1D [5]. Results from recent studies have indicated a causal association of rs7574865 single nucleotide polymorphism in the STAT4 gene with various autoimmune diseases [6]. The reference of rs7574865 polymorphism to T1D is less commonly studied [7-13], and the molecular mechanisms that underlie inherited susceptibility toward T1D remain unclear. In this study, we decided to assess the association between STAT4 rs7574865 polymorphism and T1D risk by meta-analysis.

Materials and methods

Publication search

The electronic databases PubMed, Embase, CNKI, and Web of Science (ISI) were searched using the following terms: “STAT4 or signal transducer and activator of transcription 4” in combination with “type 1 diabetes or T1D” and “polymorphism or variant or mutation”. Additional studies not captured by our data-

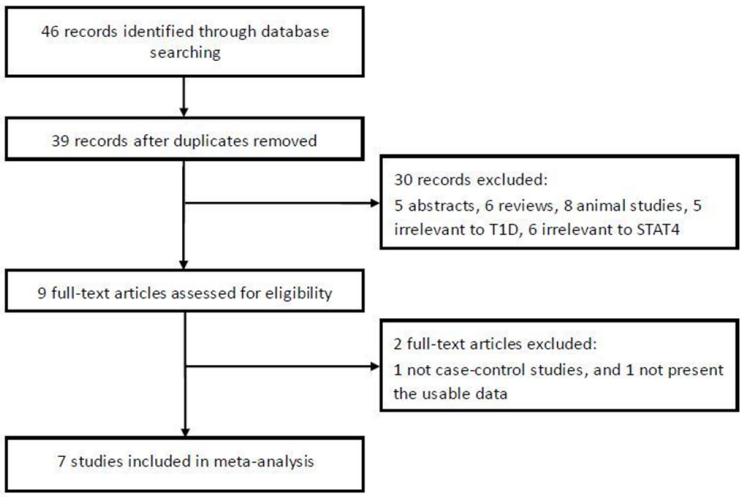

Figure 1. Flow of study identification, inclusion, and exclusion.

base searches were identified through reviewing the reference lists of retrieved articles.

Inclusion and exclusion criteria

All selected studies complied with the following two criteria: (1) case-control study on the STAT4 rs7574865 polymorphism and T1D risk; (2) sufficient published data for estimating the odds ratio (OR) with 95% confidence interval (CI). Studies were excluded if one of the following existed: (1) not relevant to T1D or STAT4, (2) not designed as case-control studies, (3) genotype frequencies or number not offered, (4) animal studies, (5) editorials, reviews and abstracts, and (6) overlapping studies.

Data extraction

Data were extracted independently and entered into separate databases from each qualified study: first author's last name, publication date, population ethnicity, mean age of patients, gender, sample size, and genotyping method.

Qualitative assessment

Two authors completed the quality assessment independently. The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality. Discrepancies were resolved by consensus and discussion.

Statistical analysis

The strength of the associations between the STAT4 rs7574865 polymorphism and T1D risk in allele model was measured by ORs and 95% CIs. The random-effects model was used. The statistical significance of summary OR was determined with *Z* test. Between-study heterogeneity was assessed by Chi-square test, and was quantified using the I^2 statistic (ranging from 0 to 100%), which was defined as the percentage of the observed between-study variability that is due to heterogeneity rather than chance. To evaluate the ethnic-specific and age-specific effects, subgroup analyses were performed. Publication bias was assessed by funnel plots and Egger's test. All statistical tests were performed by using STATA 11.0 software (Stata Corporation, College Station, TX). A *P* value of <0.05 was considered significant. All the *P* values were two-sided.

Results

Study characteristics

After a comprehensive literature search applying our inclusion criteria, 7 relevant studies which comprised 23438 subjects were identified in the final analysis (**Figure 1**). There were 4 studies with Caucasians and 3 studies used Asians. There was only one study with adults, while the rest of the studies included children. Three genotyping methods were applied, such as TaqMan, polymerase chain reaction, and SnaPShot. The quality scores ranged from 7 to 9. The main study characteristics are summarized in **Table 1**.

Quantitative data synthesis

A significant association was found between STAT4 rs7574865 polymorphism and T1D risk (OR=1.30; 95% CI, 1.13-1.48; *P*<0.01; I^2=73%; **Figure 2**). Results of this meta-analysis are showed in **Table 2**. Significant associations were also found in Asians (OR=1.33; 95% CI, 1.04-1.71; *P*=0.02; I^2=60%) and Caucasians (OR=1.26; 95% CI, 1.08-1.47; *P*<0.01; I^2=74%), respectively. This association was also positive in the pediatric patients (OR=1.41; 95% CI, 1.19-1.68; *P*<0.01; I^2=46%). Moreover, we found that STAT4 rs7574865 polymorphism was associated with early-onset T1D risk (OR=1.43; 95% CI, 1.16-1.77; *P*<0.01; I^2=0%).

Table 1. Characteristics of the studies

Author	Race	Mean age	Gender	Sample size	Genotyping method	Quality score
Lee/2008	Asian	11.79	Mixed	389/152	TaqMan	8
Martinez/2008	Caucasian	15	Mixed	311/716	TaqMan	8
Zervou/2008	Caucasian	13.7	Mixed	101/203	PCR	7
Fung/2009	Caucasian	NA	Mixed	8010/9733	NA	9
Howson/2011	Caucasian	33.3	Mixed	590/938	TaqMan	8
Park/2011	Asian	7.5	Mixed	418/1060	TaqMan	8
Bi/2013	Asian	16.3	Mixed	410/407	SNaPShot	7

PCR, polymerase chain reaction; NA, not available.

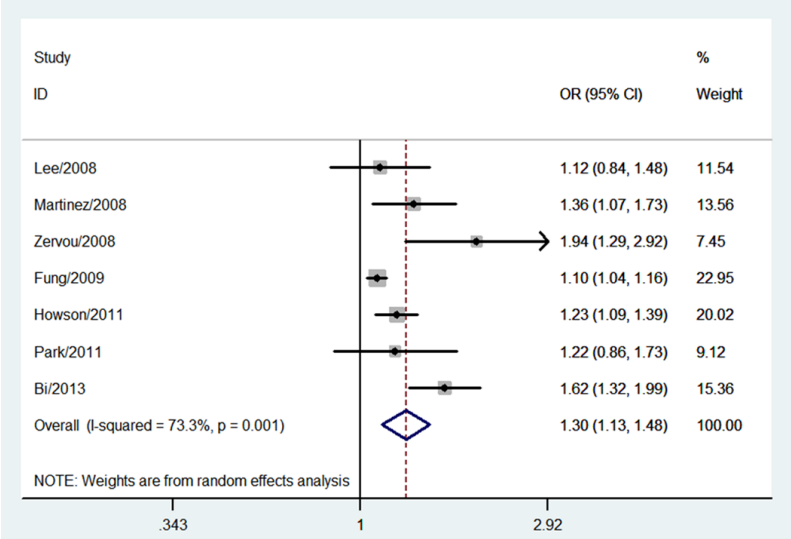

Figure 2. Forest plot of the association between STAT4 rs7574865 polymorphism and diabetes risk.

Table 2. Results of meta-analysis and subgroup analysis

Subgroup	OR (95% CI)	*P* Value	I^2 (%)
Overall	1.30 (1.13-1.48)	<0.01	73
Asian	1.33 (1.04-1.71)	0.02	60
Caucasian	1.26 (1.08-1.47)	<0.01	74
Children	1.41 (1.19-1.68)	<0.01	46
Early-onset	1.43 (1.16-1.77)	<0.01	0

The publication bias of the included studies was assessed by the funnel plot and Egger's test. The funnel plot showed no evidence for asymmetry (**Figure 3**). Egger's linear regression test showed no significant publication bias was observed (*P*=0.22).

Discussion

To our knowledge, this was the most comprehensive meta-analysis which investigated the association between STAT4 rs7574865 polymorphism and T1D risk. We found that STAT4 rs7574865 polymorphism contributed to develop T1D. In the subgroup analysis by ethnicity, we noted that Caucasians and Asians who STAT4 rs7574865 polymorphism had increased T1D risk. This result suggested that STAT4 rs7574865 polymorphism could influence T1D risk in different genetic backgrounds. In the age subgroup, we also found a significant association between STAT4 rs7574865 polymorphism and T1D risk in children. This result indicated that STAT4 rs7574865 polymorphism may play a role in the development of pediatric T1D. Furthermore, we also found STAT4 rs7574865 polymorphism was associated with early-onset T1D risk.

STAT4 is expressed in activated peripheral blood monocytes, dendritic cells, and macrophages at sites of inflammation in human beings [14]; it lies in the signaling pathway of several important cytokines, including IL-12 and type 1 interferon, as well as IL-23 [15]. STAT4 mediates IL-12 signaling that is critical for the development of protective immunity in intracellular infection. The mechanism of STAT4-mediated IL-12 signaling in such protection is dependent on the induction of Th1 responses and INF production [16].

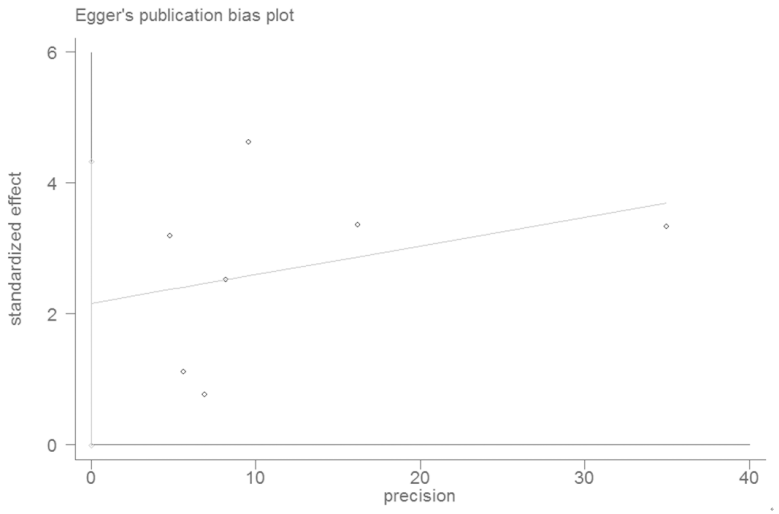

Figure 3. Funnel plot for testing the publication bias.

The present meta-analysis had several limitations. First, due to lacking of the original data of the eligible studies, we could not perform other subgroup analyses based on gender, lifestyle, and so on. Second, the numbers of published studies were not sufficient for a comprehensive analysis, particularly for Africans. Third, because small negative studies are less likely to published, the possibility of publication bias cannot be ruled out completely, even though the Egger's test and funnel plots did not provide any evidence of publication bias in this meta-analysis.

This meta-analysis suggested that the STAT4 rs7574865 polymorphism may be associated with T1D development. Further studies with a larger sample size are needed to further assess the presence of an association.

Disclosure of conflict of interest

None.

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